SHURLY (E.L.)

The Address on Medicine.

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THE ADDRESS ON MEDICINE.

Mr. President and Members:—As it would be improper on this occasion to attempt even a mention of the vast number of interesting and instructive ideas and observations connected with the science and practice of medicine, which has been evolved during the past year, I shall present for your attention only some points bearing on

THE RELATION OF MICROÖRGANISMS AND TOXINES TO THE SO-CALLED ZYMOTIC OR INFECTIOUS DISEASES,

and as this subject in its various ramifications is too vast for a detailed consideration, I must of necessity confine myself, in great measure, to a generalization upon the biological and chemical features involved. While laboratory work has done perhaps more than any other branch of science toward clearing up many vexed questions about physiological and pathological activities, yet to be of lasting value and guidance it must agree with general and clinical observations. While this has been the case more often than otherwise, yet there are instances where laboratory observations and clinical data have crossed swords!

Before proceeding to an examination of the topics mentioned, it will be necessary for us to keep in mind the fact, that the organized animal body is composed of, and is under, the operation

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(the same as other bodies) of the three elements of the Universe, Ether, Energy and Matter, under various forms and methods of combination; to which may be added what is known as "Vital Force," which some scientists regard as "energy of position" from the combustion of food. Also that this fact applies to a condition of *disease* as well as health! For in Somatic death, even, *i. e.*, death of the whole body, there are certain elemental tissues which die first, such as the blood and parenchymatous tissue, while certain other tissues, such as the epithelial, resist for a time, at least, the destructive or resolving power of Kinetic Chemical energy. In fact, the only difference between life and death from a physical point of view, consists of changes in the molecular or atomic arrangements under the direction of chemical, calorific, or electric energies. For *matter* and *energy* are indestructible! As Shelley says, "I change, but I cannot die."

To understand at all, the range of pathology and pathological chemistry,—to which we must undoubtedly look for the solution of many of the problems of the present day, it will be proper to take a brief survey of physiology and animal chemistry, which may be considered the foundation stones of our art.

To sum them up according to Mills, Foster and Kirk, we have

The Proximate Principles, which are:

- Organic
  - Nitrogenous—Proteids.
  - Non-nitrogenous
    - Certain Crystalline bodies.
    - Sugars (Carbo-hydrates),
    - Fats (Hydro-carbons).
- The Inorganic
  - Mineral salts.
  - Water.

The proteids are the chief constituents of living tissues, including the blood and lymph.

The molecule is highly complex, consisting of a great number of atoms, and is formed of the elements C.H.N.O.S. and P., although some chemists think that we are still in ignorance of its exact molecular constitution. The proteids are amorphous and non-diffusible, excepting the peptones. They are soluble in strong acids and alkalies with change of properties and constitution. In general, they are coagulated by alcohol, ether and heat. They may be classified into:

Native Albumins: Egg-albumin, serum-albumin.

Derived Albumins (albuminates): Acid-albumin, alkali-albumin, including syntonin (from muscle), para-peptone, and casein.

Globulins: Globulin, paraglobulin, fibrinogen, myosin, vitellin, globin.

Fibrin: Coagulated proteids.

Peptones: By the decomposition of proteids (albumin) by digestion with pepsin we obtain: Antialbumose, anti-peptone; and with trypsin, hemi-albumose, hemi-peptone, leucin and tyrosin.

By decomposition with acids, we get with hydrochloric acid: antialbumate, antialbumid, hemialbumose and hemipeptone.

And with *sulphuric acid* we get antialbumid, hemialbumose, hemipeptone, leucin and tyrosin, and lardacein (an amyloid substance).

The nitrogenous, non-crystalline bodies allied to proteids are: mucin, chondrin, gelatin (or gluten), elastin, keratin, nuclein, chitin.

Carbo-hydrates (Sugars): Dextrose, maltose, lactose, inosit, dextrin, glycogen, tunicin.

Fats, Fatty Acids, etc.: Formic acid, propionic acid, acetic acid, butyric acid, valerianic acid, caproic acid, capric acid, caprylic acid, laurostearic acid, myristic acid, palmitic acid, stearic acid.

The Oleic (Acrylic) Acid Series: Oleic acid.

The Neutral Fats: Glycerin.

The Glycocholic Acid Series: Glycol.

The Lactic Acids:

Bibasic Acids (Oxalic Acid Series): Oxalic acid, succinic acid.

The complex nitrogenous fats (which are obtained from nerve tissues) such as lecithin, glycerin, phosphoric acid, protagon, neurin, cerebrin.

The Series of Bile Acids, etc.: Cholic (or cholalic) acid, glycocholic acid, taurocholic acid, and cholesterin; which has been said to be the only free alcohol formed in the body.

The Bile Pigments: Bilirubin, biliverdin, choletelin, hydrobilirubin.

The Pigments of Urine: Urobilin, uroerythrin.

The Indigo Series: Indican, indigo, indol, skatol.

The Nitrogenous Metabolites: Urea, urea nitrate, uric acid, creatin, creatinin, allantoin, hypoxanthin (sarkine), xanthin, carmin, guanin, kynurenic acid, glycin, taurin, leucin, asparagin, amido succinamic acid, aspartic acid, glutaminic acid and cystin (an amido-acid).

The Acids of the Benzine, or Aromatic Series: Benzoic acid, hippuric acid, phenol, tyrosin.

In addition, we must include the leucomaines, for the discovery of which we are chiefly indebted to Gautier.

According to Vaughn and Novy there are three groups, which they classify as follows:

The uric acid group, in which they enumerate ten bases. The creatinin group, consisting of seven bases, and a third, undetermined group.

Besides these Brieger, Gautier, Hoppe-Seyler and others, have isolated from animal and vegetable organisms in various states of decomposition, about forty substances called ptomaines, some of which exist, and are formed, at times, in

the human economy—especially in the intestinal canal. Now, when we contemplate this vast array of physiological and pathological chemical products of the laboratory of the animal body, some of which are so noxious if retained in certain situations or are deflected from certain courses, we ought not to be surprised at the ease with which that equilibrium of the functions—called Health—may be upset; especially as the so-called civilized human being is not only an artificial animal with artificial impulses, and a great range of volitional power; but is assailed on every side by enemies of a parasitic nature, which, if successful in the "universal struggle," may greatly hinder the molecular and chemical coördination. Many thinkers have maintained that the biological were not distinctive from the chemical processes in Nature; but, although intimately connected, we must recognize the difference between the peculiarly vital character of molecular and blastic changes concerned in cellular movement, growth and development, such as Karyokenesis; and those changes which, from time to time, take place in the *composition* of the proximate principles in the nature of fermentation or oxidation, which are strictly chemical.

We know that certain irritations of a chemical, mechanical, electrical or calorific nature may be transmitted to vessels, so as to produce stasis and inflammation, or, directly to leucocytes, or other cellular elements, so as to induce other changes—degenerations—such as the albuminous, amyloid, waxy, lardaceous, caseous or hyaline. We also recognize that there are various degrees of susceptibility and resistance belonging to different tissues, and at different times under equal provocation, so that the blood, leucocytes, and other cells which under the influ-

ence of the nervous system, are the most important agents in carrying on the oxidation and nutrition of the body, may become the agents of tissue destruction. As Armory says, speaking in a general way of the nutrition and formation of healthy tissue: "We may classify these under two principal heads. That of metabolism, which comprises the whole range of transformation under the influence of chemical processes, and by means of which proteid substances undergo their many changes; and that of cell proliferation, by means of which the cells are multiplied." These metabolisms, whether of the constructive or destructive character, are chiefly performed by *functionally active cells.*

Although the question of independent trophic nerve action is still unsettled, we know that the influence of the vaso-motor system over the blood and nutrition is very great; for strong external stimuli, such as shock, etc., will produce changes of a physical character in the blood. Wertheim found that the blood of animals which had suffered severely from extensive burns showed afterwards the presence of foreign bodies—yellowish granules, besides increased fluidity, and disintegration of the red blood corpuscles.

Concerning animal chemistry there is but comparatively little known! However, we have seen from the immense variety of chemical substances already discovered to be results of fermentation, or chemical action and reaction, what the probable changes are! Laboratory experiments by Kolb, Munk, Peterson of New York, Shaw and others show that electrical energy is capable of producing great chemical transformation and decomposition in organic substances, outside the body. They show also that similar changes, either primarily or secondarily, may be produced

in living tissue. These observers have thus carried into the system such substances as iodine, strychnia and quinia, in proof of which, these substances were found in the urine in twelve hours or so afterwards. Zinselli has demonstrated beyond doubt, physiological, chemical, and calorific effects upon living tissues by electrical energy—electrical osmosis—as he called it.

Protoplasm, composed of carbon, hydrogen, oxygen, nitrogen, sulphur and phosphorus, arranged into a very complex molecule, which is "the physical basis of life," as Huxley says, and which is the main substance of all animal and vegetable cells, seems capable of the widest degree of change; by "its universal and constant waste; and its repair by interstitial formation of new matter similar to the old."

"Its power to give rise to new forms similar to the parent ones by a process of division. Its manifestations of periodic change in constitution developing decay and death."

Mills, Foster and other physiologists state that protoplasm is not a single proteid substance, but a mixture of such. It contains often also starch, fat, chlorophyl, etc. The *cell* is composed of protoplasm, nuclein, plasmine and chromatine as Dr. McCallum, of Toronto (who has been investigating nutrition), calls the coloring matter of animal cells. Protoplasm under nerve influence constructs a certain substance which is antecedent to another final product, which is called a ferment. According to Vonjaksch, when fibrin or other proteids are acted upon by pepsin and hydrochloric acid at a proper temperature, etc., the proteid passes through several stages before being finally converted into peptone.

The proteid molecule seems to be split up and the albumoses are the first bodies formed. Kuhne

describes a proto-albumose, hetero-albumose, and deutero-albumose. Passing to the blood, which is such an important tissue both in health and disease, and so involved in any consideration of protoplasm, we find its chemical composition to be water, proteids, salines, fats, and extractives. The proteids being known as para-globulin, globulin, serum-albumin and fibrinogen; the principal extractives: urea, creatin, and allied bodies, sugar and lactic acid—the serum containing the alkaline salts. The different corpuscles make up from one-third to one-half the weight of the blood, and of this, the red corpuscles may be said to constitute a greater part. The colorless cells are known to contain, besides protoplasm, peculiar granules, fats, glycogen, lecithin, protagon, and other extractives. One especial interest attaches to the red corpuscles, on account of their containing, organically or intimately combined, iron.

There have been very many interesting studies in relation to the blood and nutrition, of late, which we have not the time to notice. Physiologists have, however, found different actions of globulins, para-globulins and fibrinogen in serum. The behavior of coagulation, and the action of so-called fibrin fermentation is not without interest from a pathological point of view, for we shall probably find, in the future, that in many of the general diseases, characterized by parenchymatous inflammation, such as lobar pneumonia, the disease may be due to this vital process—including chemical changes of local origin and influence; for it must strike every one who gives thought to it, that some of these diseases, at least, affecting organs are not essentially inflammations, but are diseases of the blood, as has been found by my colleague, Dr. Gibbes, in some investiga-

tions now being made upon pneumonia. What Virchow terms parenchymatous inflammation, that is, cloudy swelling or parenchymatous degeneration, met with in many febrile diseases,—especially the infectious fevers and septicæmia, and after poisoning by arsenic, phosphorus or strong mineral acids is, probably, due initially to some local change in the blood and cells of the part. Dr. W. C. Glasgow, of St. Louis, pointed out a similar pathological condition in connection with some forms of acute pulmonary diseases a few years ago.

Payne considers the granular degeneration so often accompanying febrile or inflammatory infections as a *passive* and not an *active* process, resulting from the action on the epithelium or parenchymatous elements of a part, of some injury, which, acting on the vessels and connective tissues, produces hyperæmia exudation and cell-diapedesis. Another supposition is, that these molecular changes are the consequence of the high temperature to which the tissues are subjected during febrile conditions.

Concerning the typical physiological ferments contained in the saliva, gastric juice, pancreatic juice and bile, we ought to say a word. Saliva is composed of proteids, mucous and salts. Its principal function is in reducing starchy matters of food to sugar. It produces besides dextrose and maltose, acrhrodextrine. This takes place in an alkaline solution; but a feeble acid added will be sufficient to stop the action. The active ferment of this fluid is *ptyalin*. The activity of gastric juice is due to the ferment, *pepsin*. The exact nature of the process by which proteid is changed to peptone is not known. This proteolytic action is possessed by some vegetable organisms which are said to form a para-peptone.

Bile.—In the composition of human bile we have bile salts, soap and fats, cholesterin, lecithin and glycocholates, and taurocholates, also waste products, such as *hæmoglobin* and cholesterin. The digestive action of bile consists mainly of resolving mucous into a proteid and an animal gum; it also assists pancreatic fluids in the emulsifying process, and thus allows of more ready osmosis.

Pancreatic Juice.—The organic constituents are alkali albumin, peptone, leucin, tyrosin, fats and soaps, and indol. It is amylolytic, proteolytic, and steaptic. These powers are attributed to three ferments, amylopsin, trypsin, and steapsin. Proteid digestion is carried still farther than by the gastric juice, and we have a quantity of the non-crystalline nitrogen compounds formed, leucin, one of the amido groups in the fatty acid series, and tyrosin, one of the aromatic series. Now with all this biological, chemical, molecular, and fermentative action going on in the human body, forming a great number of simple and complex organic substances, not only inocuous but poisonous, being ranked as tissue, as well as functional poisons, may we not find abundant cause for disease? Peptones injected into the blood of a healthy animal, according to Brunton, will cause death. Even the healthy blood of one species of animal injected into that of another, will cause death from non-adaptability, according to Mills.

The experiments and observations of Dr. Stockton, of Buffalo, showing the deleterious effects produced by the entrance of the Portal blood into the systemic circulation is highly instructive as bearing on this point.

Microörganisms and many enzymes injected into the blood are readily destroyed, as pointed

out by Mitchell, Prudden, and others. Although there is a parasite (the filaria sanguinis hominis) which is known to inhabit the blood. Many observers believe that certain febrile states are caused by the absorption into the blood of peptones, which have gone through and not been split up by the liver into globulin. It is not improbable that absorption of ptomaines from the intestinal canal (which always contains some) may account for many of the so-called "malarial attacks" which so often serve as mantles of relief to our bewildered diagnostic sense. The proof of which may be assumed from the prompt relief which ensues from a brisk cathartic oftentimes. That dangerous condition known as ammonæmia and acetonæmia is more likely due to the absorption of ammoniæ toxines (the result of perverse chemical action) than to the presence in the blood of a special micrococcus. However, it is argued by those who have found microbes in urine, freshly voided, in that diseased condition called bacteruria, that the microörganisms are the essential cause. It is known to physiologists that after severe exercise the alkalinity of muscle juice is changed to acid, due to the presence of sarco-lactic acid. May we not see here the possibility of a combination with some organic base, so as to constitute a poison, the absorption of which determines disease. The chemical examination of sputum in various diseased states of the respiratory apparatus, shows, according to Kossell, Hoppe-Seyler, Salomon, Vonjaksch, Filehue, Stonikow, and others, the presence of peptone, serum-albumin, cholesterin, acetone, acetic, butyric, and caproic acids. Glycogen, and ferments resembling pancreatic ferments, besides a large number of different bacteria.

Bitter and Rietsch have shown that cholera mi-

crobes contain and elaborate a peptonizing ferment, and Hueppe has shown by experiment that the so-called cholera bacillus produces a toxine, the peculiar properties of which he has demonstrated on healthy animals.

The researches of Kossell show that among the decomposition products of nuclein are found guainine, which occurs in plants and vegetables. The tissue of some animals contain adenine, hypoxanthine and xanthine. Guainine and creatine are said by Vaughan and Novy to mutually replace one another. Creatine is considered by Hoppe-Seyler as an intermediate product in the formation of urea. The cholesterine, found in the body is capable of many chemical substitution products. An analysis of the thyroid gland by Bubnow gave hypoxanthine, paralactic acid, and a proteid substance which he named thryeoprotein.

Nothnagel found that the bile acids taken up into the circulation interfered with nutrition, producing fatty degeneration of organs or lymph glands. Among other poisons called by Brieger toxines, may be mentioned the so called cadaveric alkaloids, such as neuridine, cadavarine, saprine, mydaleine, putrescine, muscarine, choline, and pepto-toxines. We obtain also, from the putrefaction of albuminous matters, formic, acetic, butyric, valerianic, palmitic, acrulic, acrotomic, glycolic, lactic, valero-lactic, oxalic, glutaminic, and aspartic acids, and various ammonias, besides numerous amine bases, such as propylamine, trimethlamine, etc., also the fixed alkaloidal bases, some of which are given above. Martin and Wolfenden, by their experiments, show that the poisonous property of jequirity or abrin resides in a globulin and an albumose. They also show that peptic albumose is poisonous to dogs. They

give an interesting table of comparison of these with snake poisons. Poisonous alkaloids from articles of food have been separated by Brieger and others, in some instances, and are now recognized as probable causes of disease. The question of fermentation as set up by microörganisms and the production of enzymes and toxines by them, is a leading one, and as yet unsettled. We have seen that these processes go on in nature in all instances of decomposition and putreaction. The chemical effects may be typically illustrated by the action of toruli and other yeast fungi, which, by fermentation, produce alcohols, acetic acid, etc., from saccharine substances. Parvinski has published the clinical history of a case of asthma in a young person in which the urine contained a large quantity of acetone during the paroxysms. A similar process of fermentation has been pointed out by Brieger, Hueppe, Vonjaksch, and others in relation to the cholera bacillus, as shown by the poisonous effects on animals, by the introduction of the toxine which they had separated from the bacillus culture, and which they believe to have been produced by the bacillus. Klebs and Loeffler have also discovered that the diphtheria bacteria produces a ptomaine which may be the cause of the general infection, the microörganism being only local in its operation, a theory advocated years ago by Oertel. Loeffler could not find the bacillus in the blood, and believes that it always resides outside the body, while the toxine is the real poison.

Brieger and C. Fraenkel have shown that diphtheria bacteria produces two poisons, one of which acts toxically, while the other secures immunity. Zuegler claims to have *isolated* a poisonous crystalline alkaloid from tubercle, which he believes capable of producing the disease.

Herman Scholl, of Prague, confirms the conclusions of Brieger and Fraenkel that both anaerobic and aerobic bacteria produce poisons (toxines) or enzymes. The former more than the latter. Dr. F. Lydston, of Chicago, has shown that the evolution of venereal disease is not due to a coccus, but a ptomaine which inhabits the vagina, proving this by experiment. Many observers, however, claim to have found the coccus of gonorrhœa in the joints. There is much doubt as to the exact part played by the bacillus of typhoid fever, and without giving the controversy between Klebs, Eberth, Koch, Meyer, Friedlander, Gaffky, and others, it is probably as Benmer and Peiper say, not really pathogenic, and that the disease is produced, as Brieger suggests, by a toxine. Dr. Gibbes and myself found that sterilized watery extract of tubercle would kill a newly hatched white-fish in fifty-five seconds, completely permeating the protoplasmic mass, while an alkaline extract would do so in about sixty-five seconds. Mice afterwards injected with the fish show no signs of septicæmia or other disease, but die if injected with the same extract. Thus showing a peculiar affinity between protoplasm and tubercle toxines.

To discuss in a special manner the saphrophytic and pathogenic bacteria concerned in a full biological study would take so much time that I can only, as it were, allude to them.

In Eisenberg's tables of known bacteria for laboratory use one hundred and sixteen species are enumerated, etc.

We have found that when guinea-pigs were injected subcutaneously with the extracts made from the lungs of monkeys dead of (their) ordinary phthisis pulmonalis (which is characterized by marked emphysema) the only effects were

fever with catarrhal symptoms, lasting about two weeks. On the other hand, when injected with an extract made from tuberculous lungs from the human being, general tuberculosis followed. The morbid anatomy of the monkey lung is identical, from an ordinary view, with that of human phthisis pulmonalis. This probably illustrates the condition which all pathologists recognize now as *pseudo-tuberculosis*. I am aware that it is generally accepted that bacteria or their spores are the essential cause of most, if not all of the infective diseases. And the results of bacteriological investigation during the last few years would seem to support such a doctrine, for the following reasons, viz.: That they can be isolated by color reaction and thus directly connected with the diseased body where found. Moreover, they require a certain time for development, thus corresponding to the period of incubation of such diseases; many of them being ectogenic and saprogenic, anaerobic, or aerobic, can thus live until the opportunity for invasion offers. Being endowed with *life* and multiplying enormously, they can strenuously resist destruction. Being protoplasmic (composed of albuminous material) and microscopic they can more readily affiliate with animal fluids, cells and tissues. Existing in a passive or quiescent state as well as an active one, they can behave like vegetable seeds and spores, and preserve a long period of latency. For these, as well as other reasons which could be adduced, we are led to believe that bacteria must be the cause in some way or other of the zymotic or infectious diseases.

But the question arises, how do they accomplish this? By mere local growth for a parasitic life, by a secretion of material from themselves, in other words, are they secreting cells? or, by

inducing at once chemical changes or fermentation of a destructive character with the formation of new substances—poisons?

If we examine carefully into the basis on which certain forms of organisms stand as the materies morbi of a given disease, we shall find that those who are so strong in their faith in the essential microbic origin of disease have not in some instances looked fairly into the status of affairs. For instance, take the case of the comma bacillus of Koch, Fraenkel, in his text-book of bacteriology, third edition, says: No case of genuine cholera has as yet been reported in which the comma bacillus has been absent. From the context, he probably means in the intestines. This has been undoubtedly disproved! This illustrates again what was said at the outset, that all of these questions should be looked at without bias as far as possible, without regard to nationality, and from the stand-point of clinical as well as laboratory experience.

In whatever manner their life history is exemplified certain effects have been observed connected with them, as a class. Their career *ad interim* from one animal to another is not well known (excepting perhaps the bacillus of anthrax). Some people supposing that they may be saprogenic at first, and thence transformed to pathogenic. In the case of many of them, their spores have either never been really demonstrated to exist, or their behavior formulated. Most species, if not all, are destroyed by the healthy fluids or tissues, and hence their destiny depends upon a favorable *nidus* or *pabulum*, which means disease. It is obvious that their artificial culture in media outside the body or in the lower animals can only approximately reflect their real natural growth and development, for in no instance is it possible to

transfer the artificially cultivated microörganism to an animal with the absolute certainty that *nothing else* accompanies the bacterium. Take, for instance, tubercle bacilli, the study of which has given the most satisfactory results. We are being inoculated day by day with tubercle bacilli from the air. Why do any escape? Because some are so healthy that they are immune. But how is it that every guinea-pig inoculated gets tuberculosis? The radical believers in microbiosis say, because they are all susceptible. But the probable explanation is (like that of diphtheria), that the materies morbi is introduced and carried away by the lymphatics and sets up a general chemical change. There is also local change, abscess, at the situation of the inoculation from which are furnished spores which may flourish in the blood or lymph fluid afterward, where they will now find suitable pabulum for development, thus showing the fact that certain bacteria, at least, develope or act under certain conditions only, and upon a particular nidus. Their chemical composition is unknown during a state of activity. That certain species only appear to be pathogenic, would imply a state of specialization analogous to living nucleated cells. That their action is local, primarily, in all cases, may be assumed, because their behavior in no way shows that they themselves invade or maintain their existence in the blood or lymph fluids, because the blood would destroy them. For there are but few instances recorded of any one having found bacteria in the blood, unless we except the anthrax bacilli. Therefore it is probable that pathogenic bacteria develope only where some *previous disease* or *abnormal state* of the body suitable to them exists. That having found such, they take root, as it were, and there by catalytic action

primarily, and secondarily, give rise to a particular *toxine* or poison which in turn acts selectively as a tissue poison!

The various facts stated of a toxine connected with diphtheria, typhoid fever, cholera, suppuration and abscess (which has been shown to be independent of bacteria), croupous pneumonia, scarlatina, phthisis pulmonalis, syphilis, tetanus, gonorrhœa, cobra and other snake poisons, etc., together with the well known (chemical) noxious products forming constantly in the body, are sufficient, it seems to me, to show that the etiological agency of bacteria are *mediate* and not *immediate!*

This catalytic action coincides with clinical observations in many directions, as, for instance, the action of snake poisons, as shown by Weir, Mitchell, and the British India Sanitary Reports. From the cobra (one of the most deadly of serpents) an alkaloid as the active principle has been separated, but how far its virulence has been tested we do not know.

There are formed in certain plants, as we know, very poisonous alkaloids and glucosides, many of them corresponding in chemical character and physical behavior to animal alkaloids and colloids; solanine, for instance, is a basic glucoside which under the influence of dilute acids splits up into solanidine and sugar. Both of these active principles are blood poisons belonging to the group of sapro-toxines.

I would say that the experiments of Dr. Gibbes and myself, point to the same thing as to the nature and behavior of tubercle when cultures or extracts are introduced subcutaneously. We have also observed that the insufflation of sun-dried sputum (tubercular) will produce phthisis pulmonalis, while the inoculation of sputum (phthisis) which has been long dry from age will

not produce tuberculosis. This seems to have been confirmed by some recent experiments made by Dr. Stone in the Harvard Laboratory, who inoculated guinea pigs, with negative results, with sputum which had been long dried, and which was probably from a case of phthisis pulmonalis. We are now carrying on an investigation to ascertain the effects of inoculating guinea pigs with sputum from phthisical patients, which sputum has been dried in the sun in Southern California, under the supervision of Dr. Norman Bridge, of Chicago. The investigation has not proceeded far enough to show just what effects it will have in the production of tuberculosis, but one remarkable result has already been obtained. Six guinea pigs were inoculated, and within thirty-six hours after the operation two died of septicæmia, showing that this effect, which is a frequent result of inoculation with sputum taken directly from patients, is probably not caused by any organsim, and thus coinciding perfectly with observations which Payne gives in his text-book relating to the occurrence of septicæmia without microörganisms having been discovered in connection therewith.

Concerning the tubercle bacilli, the bacilli immediately produced in the several diseases known as tubercular, why would any previously prepared nidus be necessary? If they, or their spores (which have not as yet been satisfactorily demonstrated) are constantly invading us (which is undoubtedly true), they must at once be destroyed, or, if gaining access to the fluids of the body, would set up mechanically or otherwise, inflammation and peculiar effects as any other foreign body would. But as such microörganisms must find just the proper conditions for development or not develop, we may assume that

such conditions imply previous disease, such as caseation, whether tuberculous or not. We have already seen what complex and delicate processes attend the changes of proteids, and how easy, by radical or atomic substitution, one may be changed into the other; we can therefore see how probable it is that these microörganisms operate by a peculiar property which enables them to decompose or exercise a catalytic action on certain states and kinds of proteids. The subject of immunity and susceptibility of course cannot be discussed here—suffice it to say that the ideas and experiments of Trudeau of New York, and McLaughlin of Texas, in this direction, are worthy of careful attention, and apply not only to microbes but to chemical substances connected with them. To say nothing of the chemical action and products normally evolved, as already explained, Abelous has obtained sixteen species of microbes from the empty stomach by lavage; seven of these were well known varieties, ten of these attacked and changed albumin, twelve fibrin, and nine gluten, ten caused transformations of lactose into lactic acid; thirteen formed a variable quantity of glucose from starch; rapid and energetic decomposition with evolution of gas, leucin, tyrosin, indol, skatol and ammonia compounds took place in presence of saliva. I do not know that all of these observations have been confirmed. But we have confirmed his experiments regarding albumin, which is readily transformed by saliva in the presence of microörganisms outside the body. Experiments with invertin, a ferment found in the intestinal canal, have shown some interesting results in relation to microbe metamorphosis, which are still, however, *sub judici*. Jaccoud finds the pneumococcus, besides several other forms of bacteria, in diphthe-

ria. He believes that individual reaction is what determines the disease.

What application can be made therapeutically of the facts obtained? It is manifest that the diseases in question are caused in some way by the presence or entrance of microörganisms. Therefore the main therapeutic indication is to attack them, or neutralize their operation. We have seen that bacteria either produce for themselves or from the organic substances which they attack, a poison, or enzyme, and that this can be cultivated outside the body in some instances. Pathological chemistry has not demonstrated with exactness the nature of all of these poisons, or classified them, but it is fair to believe that such will surely take place in the near future. Although it is generally supposed that the inorganic chemicals are not tissue poisons, but act only upon the functions through the nervous system, yet we believe that such is not the case when we observe the tissue changes produced by iodine, bromine, phosphorus, arsenic, the silver, gold, platinum and cupric salts, besides some of the vegetable alkaloids. Dr. Gibbes and myself have been able to neutralize the toxic effect of tubercle by admixture with chlorine iodine. Chloride of gold combined with glycerine, salts of platinum and glycerine and peroxide of manganese, outside the body, and with the chlorine, iodine, and gold and sodium chloride in inoculated animals. That certain chemicals have a selective action on tissues cannot be doubted; take, for example, the hypodermic injection of cantharidin used a few years ago by Cornil and Ranvier, resulting in the production of inflammation of the air passages; also the work lately of Liebreich in injecting cantharadate of potassium for the cure of phthisis pulmonalis and tuberculosis, which he believes pro-

duces exudation, as when applied to the skin. Also the selective action of strychnia and atropia, the latter acting on the secretory cells of the salivary glands, stopping secretion notwithstanding the induction of hyperæmia. Arecoline, a volatile liquid alkaloid from the areca nut, has a selective action on the heart and is excreted unchanged. Harnack probably states the truth in saying that the action of drugs is molecular and fermentative. On account of the changes which remedies are apt to undergo in the stomach and intestines, by being oxidized or otherwise changed before absorption into the system, the rational way, it seems to me, is to introduce the agent hypodermically; in this way it is possible to get effects which cannot be accomplished otherwise. Dr. Lauderer has obtained beneficial effects in phthisis from hypodermic injection of balsam Peru, which he says goes at once to the diseased part, thus simulating animal fluids or cultures, as exemplified by the effects of Koch's lymph and similar cultures used before by Pasteur, Grancher, Martin, Rengi, Gibbes and others. Dr. Behring has lately found that a number of chemical substances used hypodermically, such as aurochloride of sodium, naphthaline, and trichloride of iodine, were capable of neutralizing the poison of diphtheria in guinea pigs, but the most active of all was the trichloride of iodine. He also practiced, in diphtheria the plan of vaccinating the animals with bacilli cultures. Prof. Merzolski reports much better effects from bromide of gold used hypodermically (in $\frac{1}{4}$ and $\frac{1}{2}$ gr. doses), than by the usual way of administration of bromides. The prompt effects of Sammter's treatment of erysipelas by carbolic acid injections, are well known. The superior effects of the treatment of syphilis, by hypodermic in-

jection of cyanide and bichloride of mercury and chloride of gold and sodium are striking, as we all know. Dr. Zumbali, of Rome, found hypodermic injections of chlorodyne in profuse diarrhœa particularly superior to its administration by the mouth. The hypodermic injection of ergot for the relief of hæmoptysis is another example. This agent, administered in considerable quantity by the mouth, will often fail; whereas one, or at most two, hypodermic injections of $\frac{1}{10}$ or $\frac{1}{5}$ gr. of ergotin will generally stop a severe attack. Digitalis also acts upon the cells and vascular system more certainly when so administered. I may also mention the beneficial effects of strychnia used hypodermically, in typhoid conditions. That animal poisons can be neutralized in the body, I believe, will soon be more generally demonstrated. The experience of Tyndall, of New York, in the vaccination process for the cure of tuberculosis, promises well. Hemmeter has stopped the course of diphtheria by the vaccination of the patient with an erysipelas toxine; and Prof. Grancher states that persons suffering from tenia tonsurans are immune from diphtheria. This would seem toshow that there must be a sort of antagonism or isomerism between animal and chemical poisons; and why may not more universal application be made of this principle, with a view of obtaining more specific therapeutic agents and effects? The ethereal oils, on account of their diffusable antiseptic properties, are undoubtedly applicable to the neutralization of disease when used hypodermically, and may prove yet of great value in the zymotic diseases. We are now engaged in using some of them in this way, and find that they actually provoke the liquefaction of effused products. We are also experimenting with members of the benzoin and

formic acid series, and the toluidines, in an endeavor to learn their action on metabolism and disease poisons. Dr. Emil Schutz believes that drugs act topically on the secretions by precipitating albumin. He also demonstrated, by cases, that tannic acid may produce urticaria by external application alone. Galezowski, of Paris, has lately discovered a new bacteriacide, by the decomposition of an aniline dye, which has the same properties as pyoktania on the tissues. In this direction we may look for brilliants results, on account of the action of these substances on albuminates. My chief object is to awaken a more general interest in physiological and pathological chemistry, to the end that we may as speedily as possible acquire a scientific chemical therapy, and thus release her from the dungeon of empiricism, where she has been imprisoned with so little light these many years.